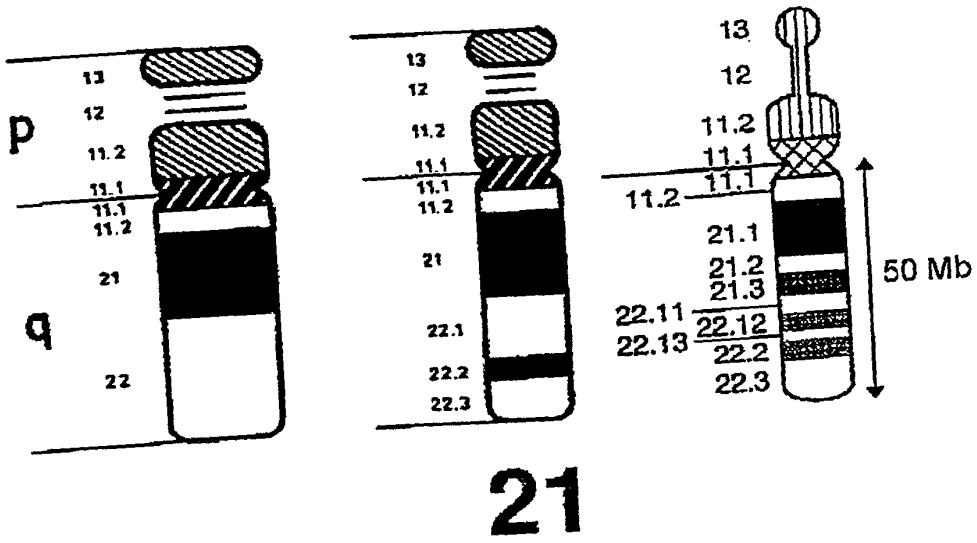


Figure 1

D5U5U8U8 : 0U5U5U4

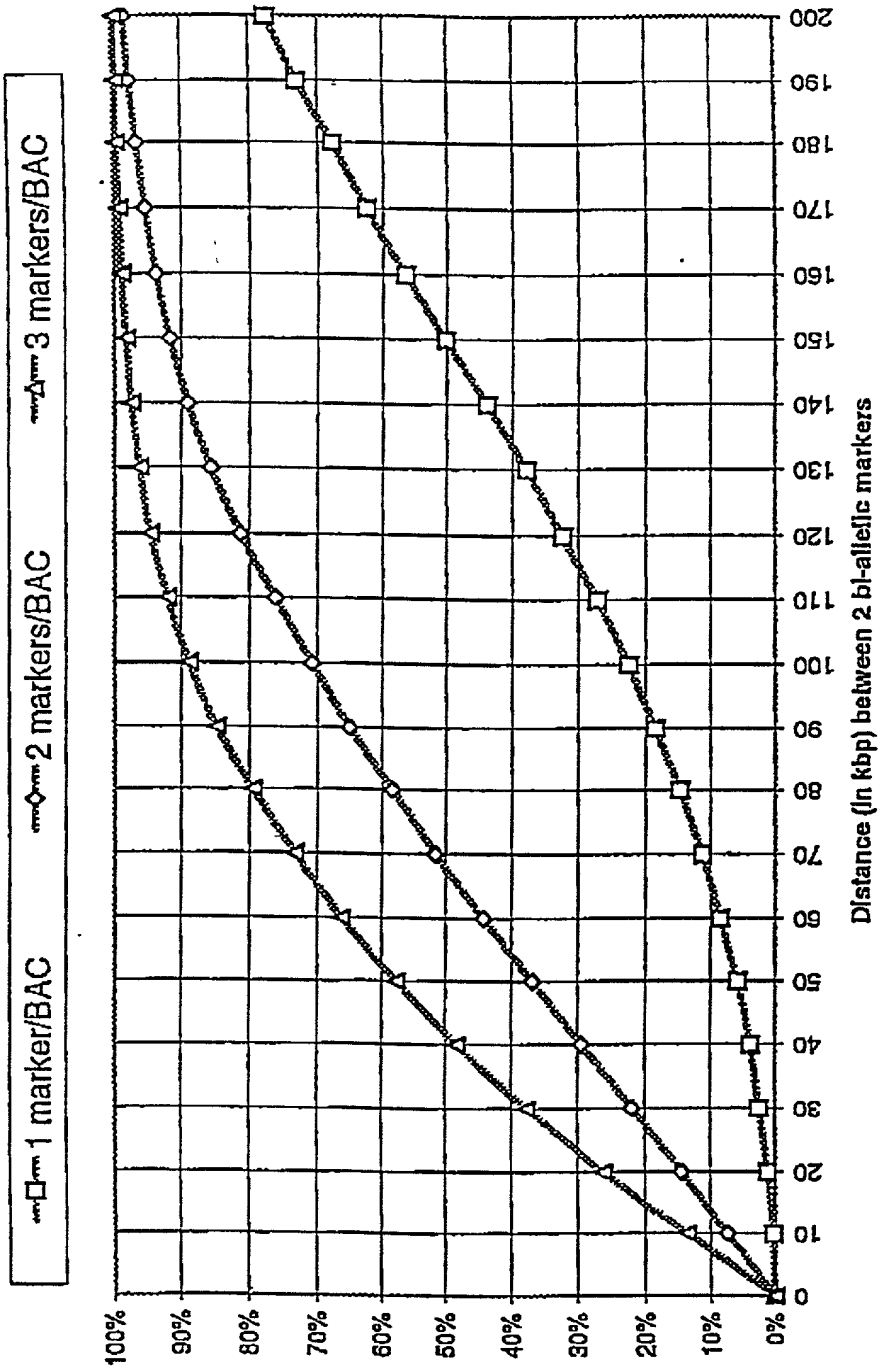

1 marker/BAC
2 markers/BAC
3 markers/BAC
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
Distance (in kbp) between 2 bi-allelic markers

Figure 2A

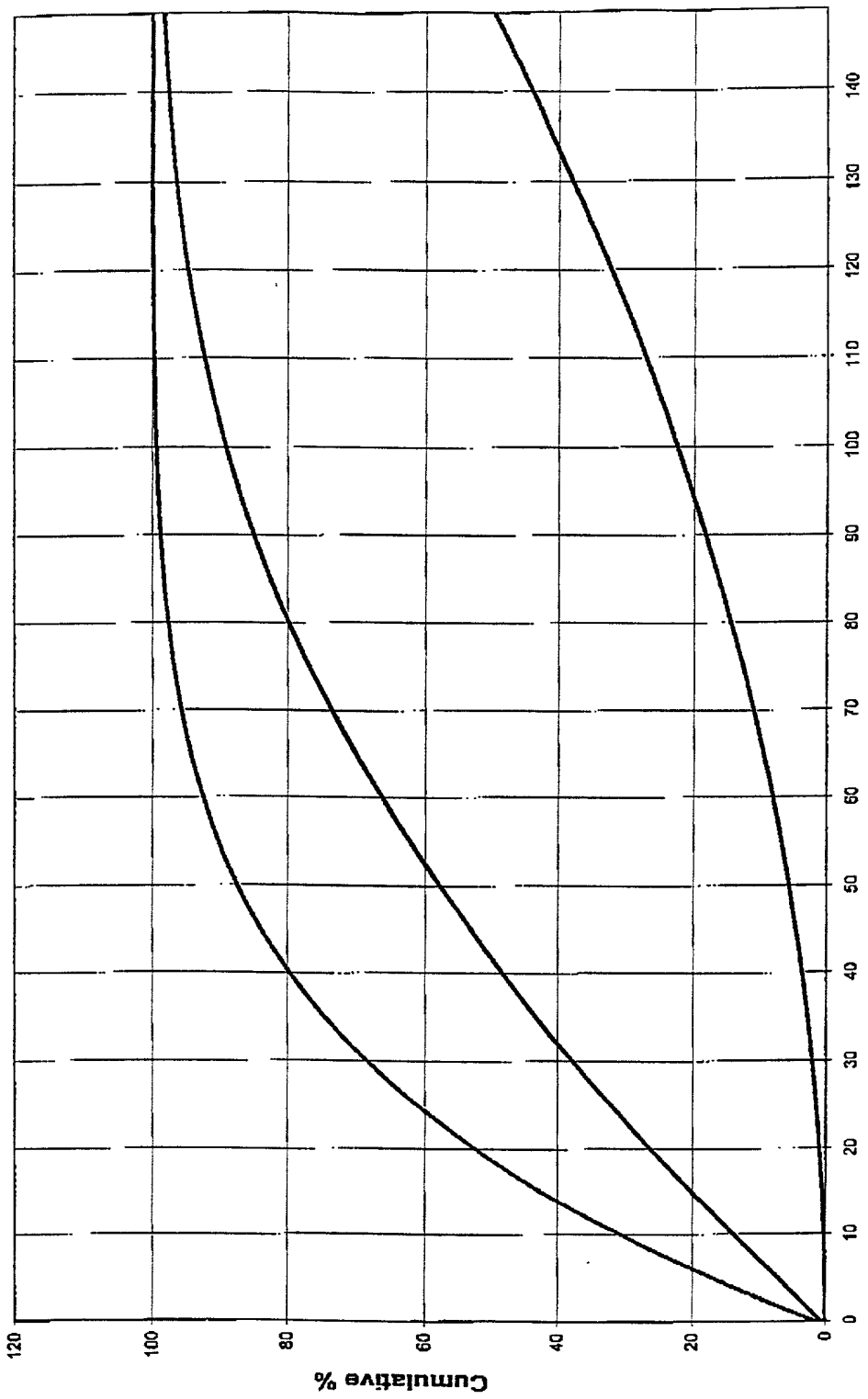
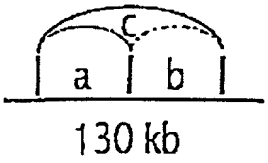

Cumulative %
120
100
80
60
40
20
0
Distance between Markers
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
1 marker/BAC
3 markers/BAC
6 markers/BAC

Figure 2B

LD in a random French caucasian population

- 54 sized « random » BACs covering 8100 kb
- 213 SNP ; 2 to 6 / BAC, mean allele frequency = 0.3
- Order and distance unknown
- For 1 BAC :



* $\overline{m}$ intermarker distance : 130/3 = 43 kb
* $\overline{m}$ LD strength estimate : m (a,b,c) = 0.51

- For 54 BACs :

* $\overline{m}$ intermarker distance = 38 kb
* $\overline{m}$ LD strength estimate = 0.63 ± 0.05 (324 pairs)

- For 19 unlinked SNPs : m LD strength estimate = 0.12 ± 0.007 (171 pairs)

Figure 2c

FR0550 : 6050550

p-VALUE DISTRIBUTION

# aff	150						
# non aff	150						
	pAi non aff	0	0,1	0,2	0,3	0,4	0,5
Δ pAi	0,05	8,77E-05	0,06407752	0,14252002	0,19106311	0,21543442	0,22009395
Δ pAi	0,1	1,91E-08	0,00060364	0,00467774	0,01023571	0,01382303	0,01382303
Δ pAi	0,15	3,06E-12	1,3319E-06	3,8827E-05	0,0001478	0,0002343	0,00020218
Δ pAi	0,2	3,22E-16	9,1413E-10	9,0305E-08	5,733E-07	9,6336E-07	5,733E-07
Δ pAi	0,25	2,08E-20	2,2614E-13	6,2679E-11	5,873E-10	8,7113E-10	2,5396E-10
Δ pAi	0,3	7,82E-25	2,152E-17	1,3261E-14	1,5189E-13	1,5189E-13	1,3261E-14
Δ pAi	0,35	1,62E-29	7,9823E-22	8,4152E-19	9,1669E-18	4,2713E-18	5,5844E-20
Δ pAi	0,4	1,73E-34	1,1282E-26	1,524E-23	1,1488E-22	1,524E-23	1,1282E-26

# aff	200						
# non aff	200						
	pAi non aff	0	0,1	0,2	0,3	0,4	0,5
Δ pAi	0,05	5,92E-06	0,03250945	0,09039173	0,13111935	0,15260313	0,15678006
Δ pAi	0,1	8,65E-11	7,4765E-05	0,00109084	0,00302686	0,00447365	0,00447365
Δ pAi	0,15	8,02E-16	2,3653E-08	2,0257E-06	1,1771E-05	2,1573E-05	1,7772E-05
Δ pAi	0,2	4,18E-21	1,5375E-12	6,7374E-10	7,764E-09	1,5417E-08	7,764E-09
Δ pAi	0,25	1,13E-26	2,525E-17	4,4025E-14	8,5532E-13	1,4423E-12	2,8149E-13
Δ pAi	0,3	1,47E-32	1,1488E-22	5,8424E-19	1,4886E-17	1,4886E-17	5,8424E-19
Δ pAi	0,35	8,62E-39	1,4784E-28	1,5457E-24	3,6958E-23	1,3394E-23	4,197E-26
Δ pAi	0,4	2,09E-45	5,2308E-35	7,6438E-31	1,1224E-29	7,6438E-31	5,2308E-35

# aff	affected individuals
# non aff	non affected individuals
pAi non aff	allele frequency in non affected individuals
Δ pAi	% Difference in allele frequency between affected and non-affected individuals

Figure 3 (I)

p-VALUE DISTRIBUTION

# aff	500						
# non aff	500						
	pAi non aff	0	0,1	0,2	0,3	0,4	0,5
Δ pAi	0,05	8E-13	0,00072323	0,00741965	0,0169842	0,02371865	0,02516449
Δ pAi	0,1	1,07E-24	3,7948E-10	2,4176E-07	2,7579E-06	6,9679E-06	6,9679E-06
Δ pAi	0,15	3,81E-37	1,0719E-18	5,8344E-14	4,2622E-12	1,8601E-11	1,1611E-11
Δ pAi	0,2	2,96E-50	5,0895E-29	1,6881E-22	6,9321E-20	3,7441E-19	6,9321E-20
Δ pAi	0,25	4,27E-64	7,2043E-41	7,7528E-33	1,194E-29	4,3462E-29	7,6438E-31
Δ pAi	0,3	9,7E-79	3,9328E-54	6,3017E-45	1,9429E-41	1,9429E-41	6,3017E-45
Δ pAi	0,35	2,91E-94	8,8513E-69	8,7879E-59	2,3478E-55	1,8839E-56	1,1206E-62
Δ pAi	0,4	9,5E-111	7,7199E-85	1,8063E-74	1,4484E-71	1,8063E-74	7,7199E-85

# aff	150						
# non aff	850						
	pAi non aff	0	0,1	0,2	0,3	0,4	0,5
Δ pAi	0,05	2,16E-20	0,00994614	0,04896055	0,08358651	0,10417953	0,11025423
Δ pAi	0,1	2,01E-39	5,571E-07	0,00010149	0,00058665	0,00119145	0,00139743
Δ pAi	0,15	1,11E-58	2,7555E-13	8,462E-09	2,9851E-07	1,2395E-06	1,6229E-06
Δ pAi	0,2	3,27E-78	2,1683E-21	3,2211E-14	1,1049E-11	1,111E-10	1,5638E-10
Δ pAi	0,25	4,96E-98	4,4952E-31	6,5226E-21	3,1015E-17	2,5169E-16	1,1763E-15
Δ pAi	0,3	3,7E-118	3,6987E-42	8,129E-29	6,9335E-24	5,4331E-22	6,5657E-22
Δ pAi	0,35	1,4E-138	1,6797E-54	7,1058E-38	1,2938E-31	2,9415E-29	2,5869E-29
Δ pAi	0,4	2,4E-159	5,4915E-68	4,8846E-48	2,1003E-40	1,3332E-37	6,8178E-38

# aff	affected individuals
# non aff	non affected individuals
pAi non aff	allele frequency in non affected individuals
Δ pAi	% Difference in allele frequency between affected and non-affected individuals

Figure 3 (II)

Title: METHODS, SOFTWARE AND APPARATI FOR IDENTIFYING GENOMIC REGIONS HARBORING A GENE ASSOCIATED WITH A DETECTABLE TRAIT
Inventors: Nicholas SCHORK, et al.
Assignee: Genset Corporation
Our Ref.: 55.US4.DIV
6/31

p-VALUE DISTRIBUTION

# aff	200						
# non aff	500						
	pAi non aff	0	0,1	0,2	0,3	0,4	0,5
Δ pAi	0,05	1,06E-12	0,00789803	0,03942584	0,06867566	0,08621572	0,09083704
Δ pAi	0,1	3,45E-24	4,4217E-07	5,6883E-05	0,00031976	0,0006363	0,00070881
Δ pAi	0,15	5,9E-36	4,3025E-13	3,3635E-09	9,2134E-08	3,319E-07	3,5871E-07
Δ pAi	0,2	4,73E-48	1,5566E-20	1,0346E-14	1,7218E-12	1,1512E-11	1,0047E-11
Δ pAi	0,25	1,67E-60	3,5436E-29	2,0473E-21	2,2178E-18	1,1498E-17	1,3524E-17
Δ pAi	0,3	2,46E-73	7,2498E-39	3,0748E-29	2,0601E-25	3,4525E-24	7,4807E-25
Δ pAi	0,35	1,44E-86	1,6945E-49	3,9559E-38	1,4118E-33	2,662E-32	1,4118E-33
Δ pAi	0,4	3,2E-100	5,3051E-61	4,7325E-48	7,1282E-43	1,0691E-41	7,2652E-44

# aff	500						
# non aff	1000						
	pAi non aff	0	0,1	0,2	0,3	0,4	0,5
Δ pAi	0,05	6,48E-24	5,7827E-05	0,00172627	0,00551541	0,00882876	0,00978249
Δ pAi	0,1	6,53E-47	3,065E-14	1,0301E-09	4,3205E-08	1,8833E-07	2,2731E-07
Δ pAi	0,15	1,2E-70	2,0716E-27	3,7441E-19	4,6626E-16	6,9719E-15	6,9719E-15
Δ pAi	0,2	3,33E-95	1,1636E-43	1,6614E-31	8,5632E-27	4,1421E-25	1,9885E-25
Δ pAi	0,25	1,2E-120	1,7683E-62	1,5329E-46	3,1722E-40	8,6765E-39	3,6071E-39
Δ pAi	0,3	5,3E-147	1,526E-83	4,2697E-64	2,5968E-56	3,9328E-54	2,5968E-56
Δ pAi	0,35	2,4E-174	1,184E-106	4,5658E-84	4,7426E-75	4,2624E-73	4,0958E-77
Δ pAi	0,4	9,4E-203	1,082E-131	2,137E-106	1,8014E-96	3,3252E-95	6,725E-102

# aff	affected individuals
# non aff	non affected individuals
pAi non aff	allele frequency in non affected individuals
Δ pAi	% Difference in allele frequency between affected and non-affected individuals

Figure 3 (III)

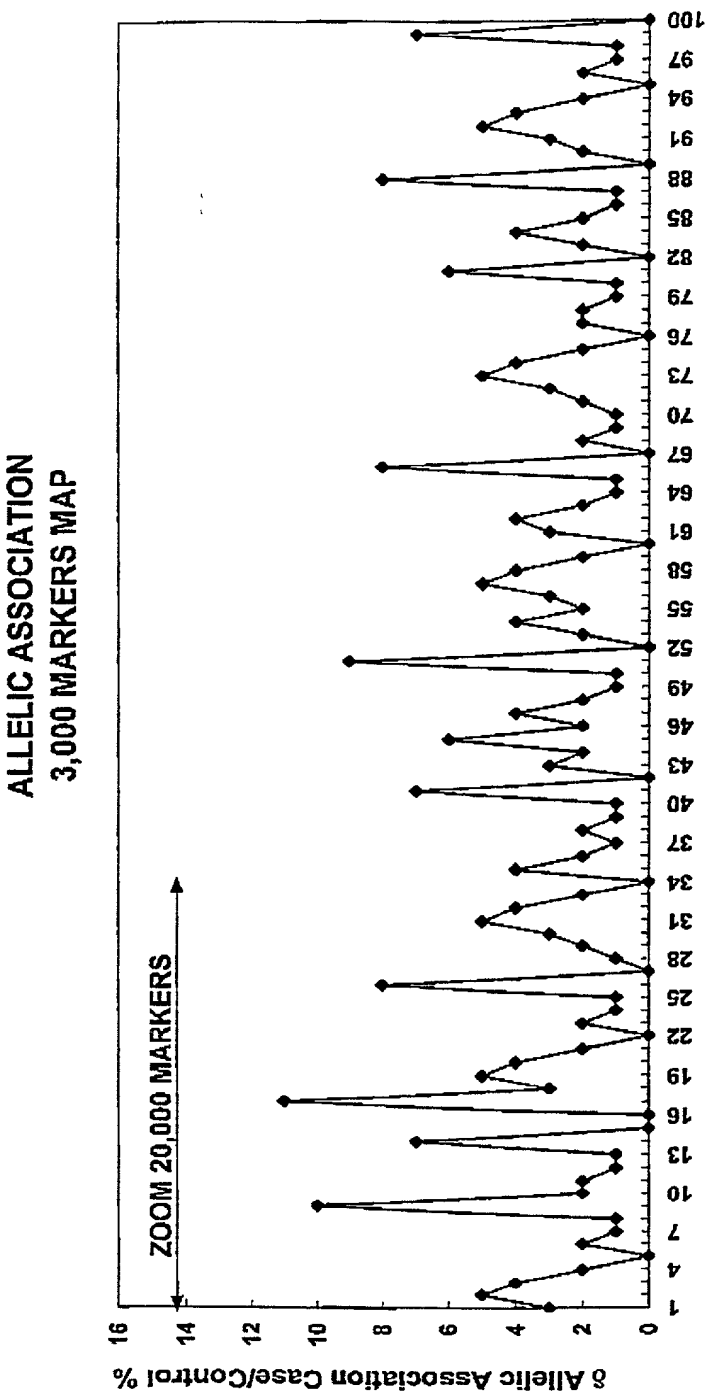

ALLELIC ASSOCIATION
3,000 MARKERS MAP
ZOOM 20,000 MARKERS
δ Allelic Association Case/Control %
Marker #
0
2
4
6
8
10
12
14
16
1
4
7
10
13
16
19
22
25
28
31
34
37
40
43
46
49
52
55
58
61
64
67
70
73
76
79
82
85
88
91
94
97
100

Figure 4

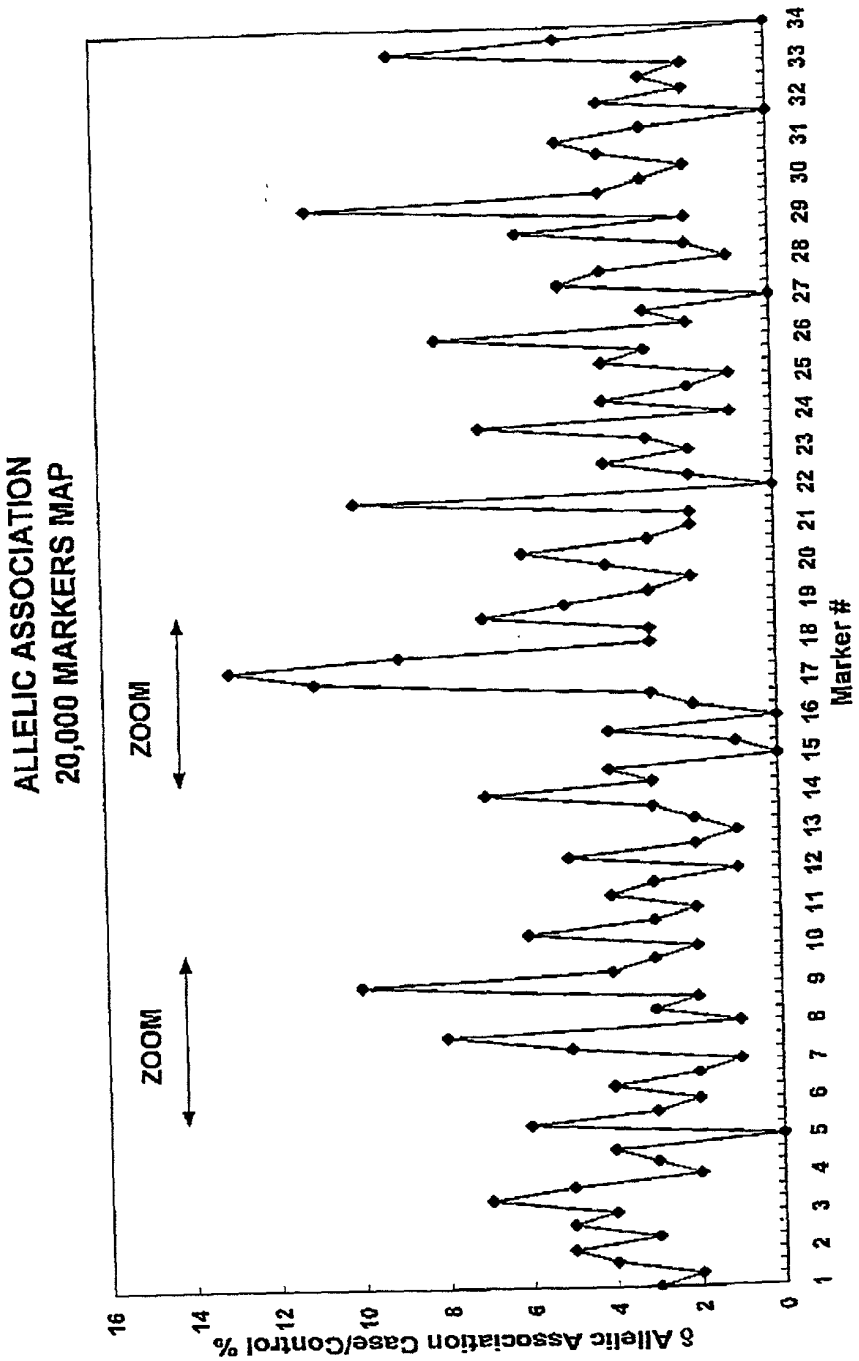


Figure 5

D9858260 - 050404

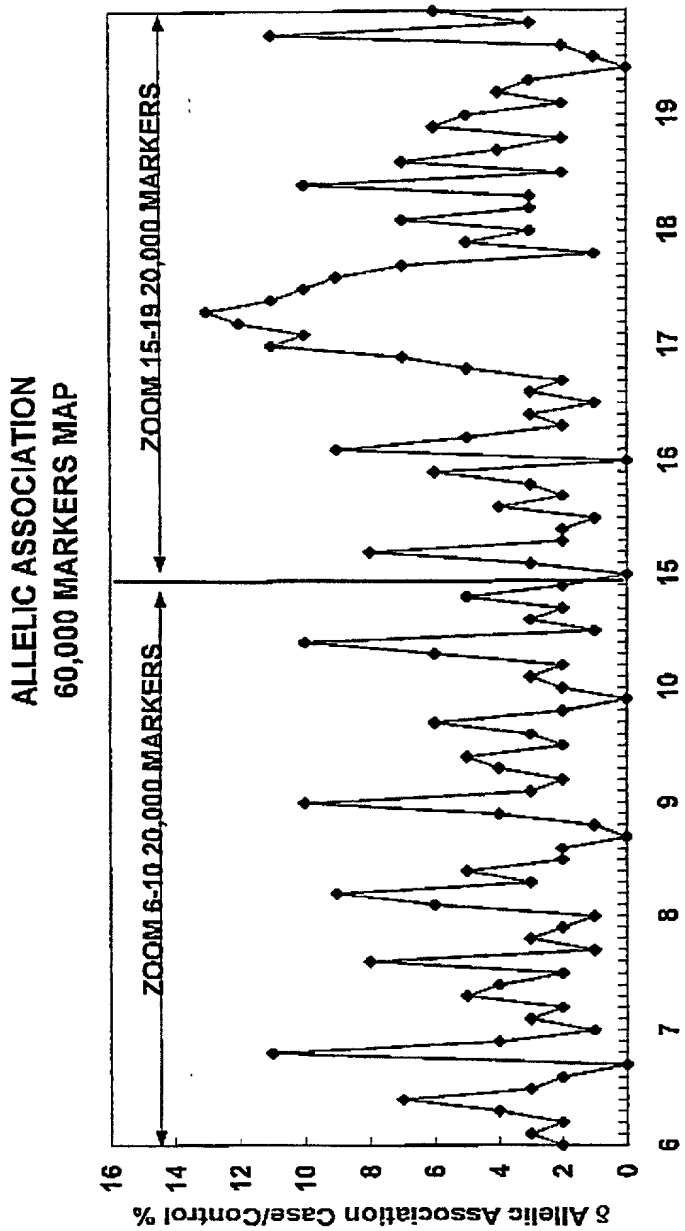


Figure 6

PCT/US98/26850

TOSTSO" 68295860

Title: METHODS, SOFTWARE AND APPARATI FOR IDENTIFYING GENOMIC REGIONS HARBORING A GENE ASSOCIATED WITH A DETECTABLE TRAIT
Inventors: Nicholas SCHORK, et al.
Assignee: Genset Corporation
Our Ref.: 55.US4.DIV
11/31

APO E REGION HAPLOTYPE FREQUENCY ANALYSIS

POPULATIONS	AD CASES (225)	AD CONTROLS (248)

markers	99-366	99-344	99-359	99-355	haplotype frequencies		odds-ratio	P value
p value	3,01E-01	1,11E-01	6,63E-01	1,38E-01	cases	controls		
haplotype 1	C	G			0,404	0,308	1,52	3,05E-03 ***
haplotype 2		G	A		0,203	0,165	1,29	1,24E-01 *
haplotype 3			G	G	0,375	0,306	1,36	2,83E-02 **
haplotype 4	C		A		0,264	0,209	1,36	5,95E-02 **
haplotype 5		G		A	0,115	0,071	1,70	1,64E-02 **
haplotype 6	C			A	0,15	0,129	1,19	3,59E-01 *
haplotype 7	T		G	G	0,225	0,122	2,09	4,76E-05 *****
haplotype 8	T	A	G	G	0,228	0,108	2,44	2,05E-06 ******

Figure 7

FP05T5P0 : 9525252

APO E REGION HAPLOTYPE SIMULATION
POPULATION : 225 CASES vs 248 CONTROLS

Haplotype #	4 Markers				haplotype frequencies		odds-ratio	pvalue
	99-344/439	99-366/274	99-359/308	99-355/219	cases	controls		
	A	T	G	G	0,228	0,108	2,44	2,05E-06 ******

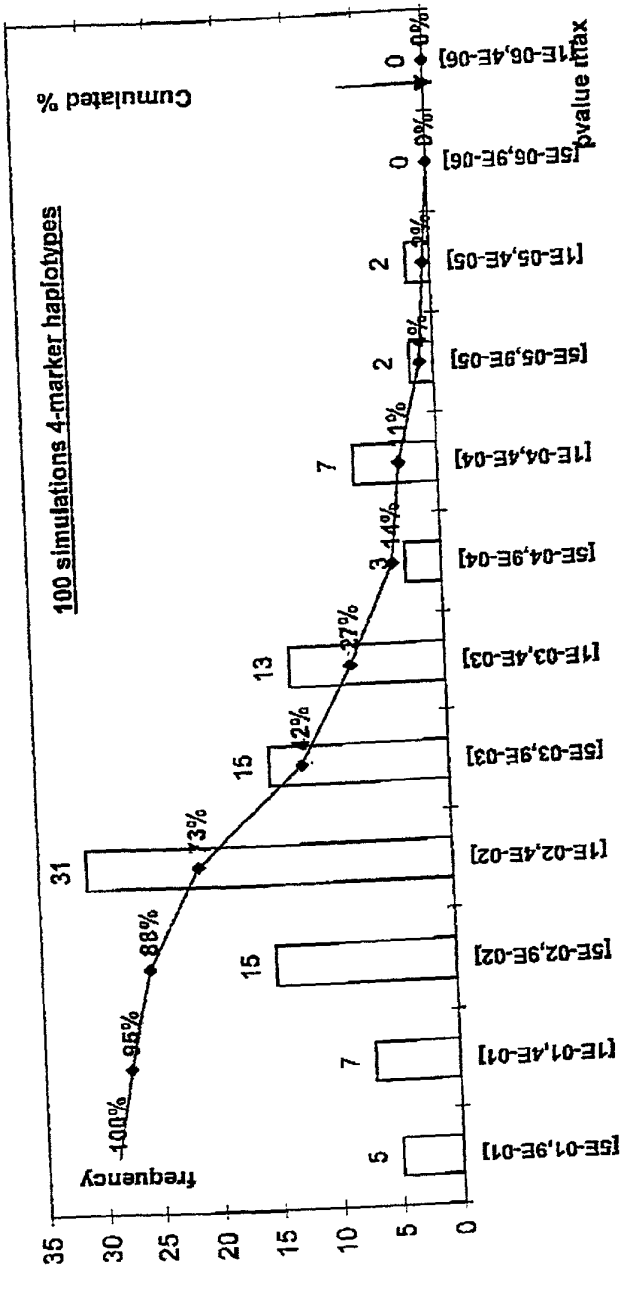


Figure 8

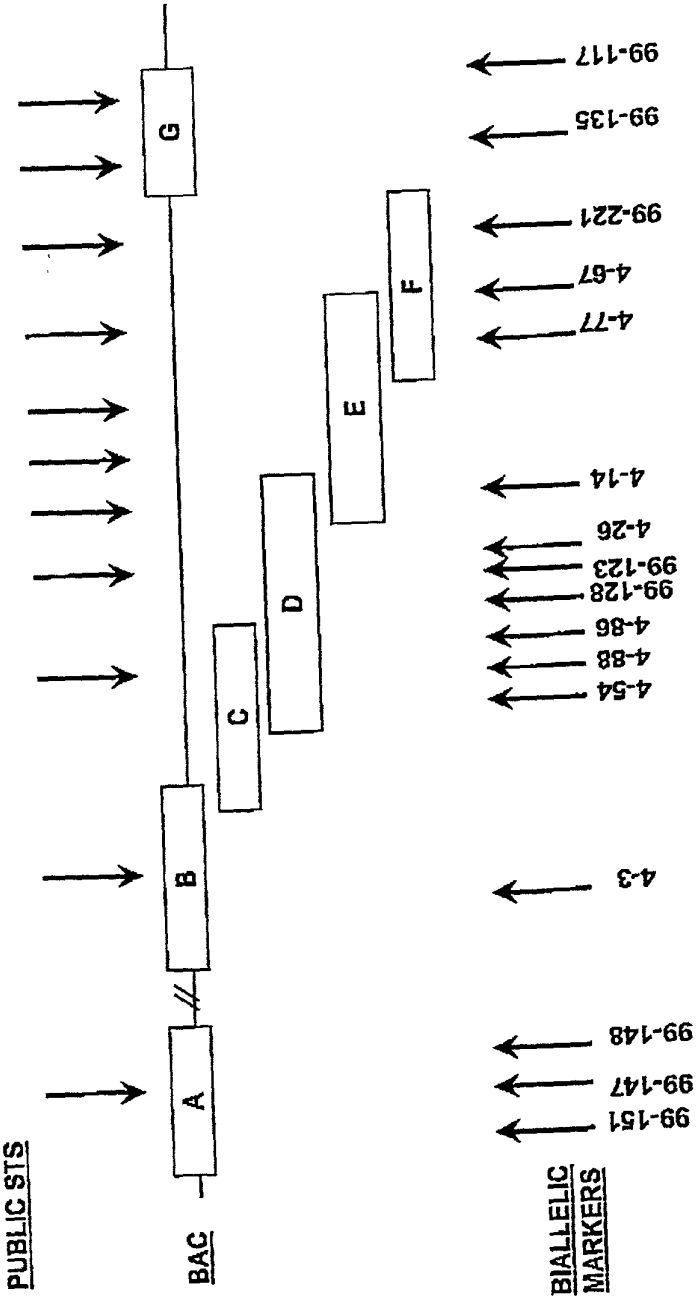


Figure 9

09528285 - 051501

TOSTSO"68283860

PROSTATE CANCER ASSOCIATION STUDIES (FIRST SCREENING)

Population Sample size	PROSTATE CANCER CASES = 112	NON AFFECTED CONTROLS=76
Population Characteristics	35 sporadic cases + 77 familial cases	> 65 years PSA<4

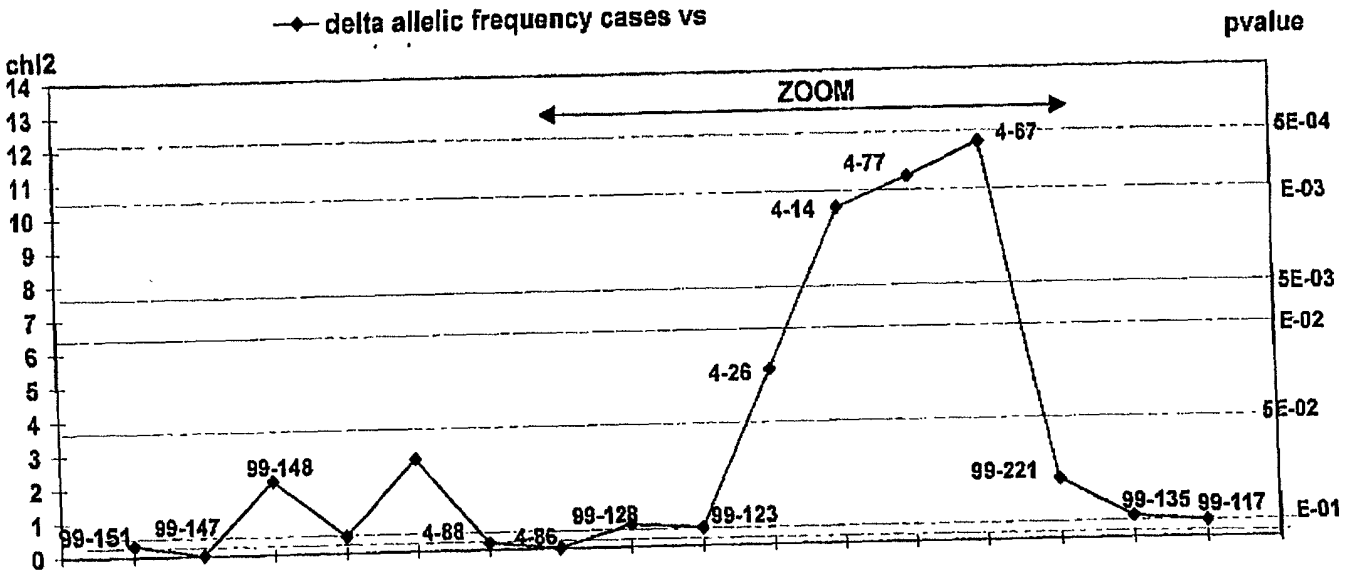


Figure 10

METHODS AND APPARATUS FOR IDENTIFYING GENOMIC REGIONS HARBORING A GENE ASSOCIATED WITH A DETECTABLE TRAIT
Inventors: Nicholas SCHORK, et al
Assignee: Genset Corporation
Our Ref.: 55.US4 DIV
14/31

PROSTATE CANCER ASSOCIATION STUDIES (ZOOM)

	PROSTATE CANCER CASES (185)	NON-AFFECTED CONTROLS (104)
characteristics of populations	47 sporadic cases + 138 familial cases	> 65 years PSA<4

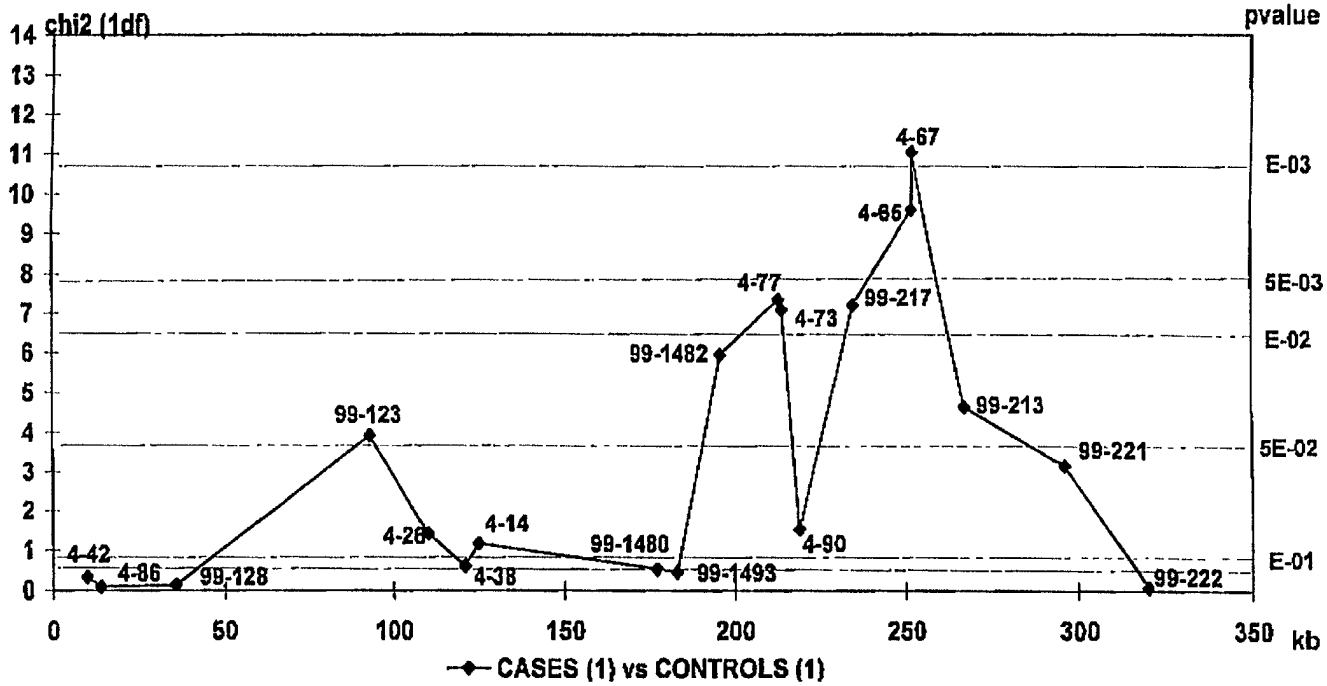


Figure 11

Title: METHODS, SOFTWARE AND APPARATUS FOR IDENTIFYING GENOMIC REGIONS HARBORING A GENE ASSOCIATED WITH A DETECTABLE TRAIT
Inventors: Nicholas SCHORK. et al.
Assignee: Genset Corporation
Our Ref.: 55 US4 DIV
15/31

PROSTATE CANCER HAPLOTYPE FREQUENCY ANALYSIS

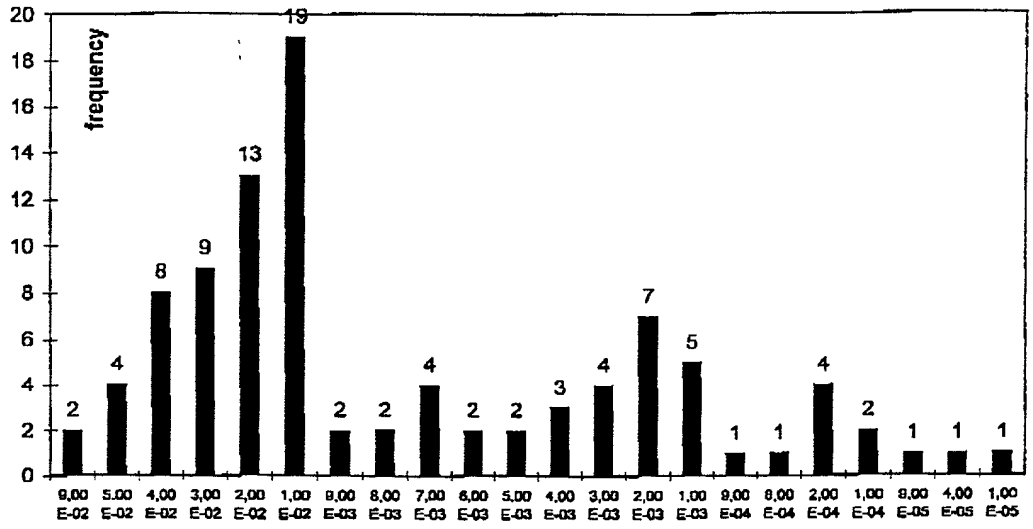
	PROSTATE CANCER CASES (281)	NON-AFFECTED CONTROLS (130)
characteristics of populations	143 sporadic cases + 138 familial cases	> 65 years PSA<4

markers	99-123	4-26	4-14	4-77	99-217	4-67	99-213	99-221	99-135	haplotype frequencies		relative risk	pvalue
bacs	H0287B09	B0189E08		B0463F01					B0725B12				
genes	<----PG1---->												
p value	2,00E-01	1,00E-01	1,00E-01	2,00E-02	2,00E-02	6,00E-04	9,00E-02	7,00E-01	2,00E-01	cases	controls		
haplotype 8 >304kb<	C	A	C	G	T	T	C	A	A	0,075	0,018	4,42	9,00E-04 ***
haplotype 7 >286kb<		A	C	G	T	T	C	A	A	0,095	0,016	6,46	6,00E-05 ****
haplotype 6 <186kb>		A	C	G	T	T	C	A		0,116	0,019	6,78	1,00E-05 *****
haplotype 5 <171kb>			C	G	T	T	C	A		0,117	0,013	10,06	9,00E-07 ******
haplotype 4 <83kb>				G	T	T	C	A		0,117	0,025	5,17	2,00E-05 *****
haplotype 3.1 <54kb>					T	T	C	A		0,117	0,027	4,78	2,00E-05 *****
haplotype 3.2 <54kb>				G	T	T	C			0,222	0,109	2,33	4,00E-05 *****
haplotype 2.2 <39kb>				G	T	T				0,251	0,134	2,17	2,00E-04 ****
haplotype 2 <32kb>					T	T	C			0,226	0,112	2,32	1,00E-04 ***
haplotype 1.1 <17 kb>					T	T				0,256	0,146	2,01	3,00E-04 ****
haplotype 1.2 <15 kb>						T	C			0,233	0,129	2,05	6,00E-04 ***

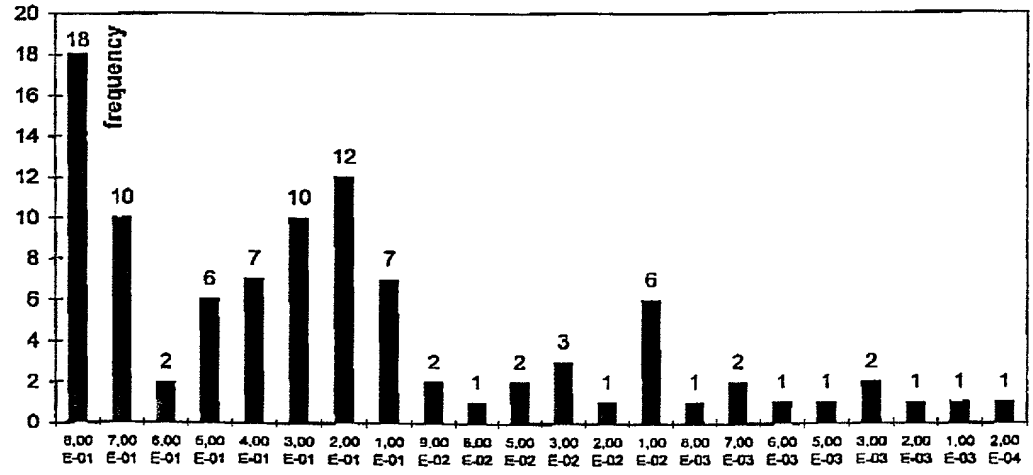
Figure 12

PROSTATE CANCER HAPLOTYPE SIMULATIONS (100 ITERATIONS)

							haplotype frequencies		relative	pvalue
markers	4-14	4-77	99-217	4-67	99-213	99-221	cases	controls	risk	
haplotype	C	G	T	T	G	A	0,117	0,013	10,06	9,00E-07



pvalue max of haplotypes for 100 simulations



pvalue of haplotype CGTTGA for 100 simulations

Figure 13

AVERAGE LD PATTERN GENOMIC HETEROGENEITY

Recombination rate	Lower A	Higher B
Nb markers	89	69
All SNP	0.61 (749)	0.42 (1190)
Rare < 0.2 Rare vs rare	0.75 (65)	0.17 (158)
Frequent > 0.2 Frequent vs frequent	0.51 (410)	0.49 (544)
Rare vs frequent	0.72 (274)	0.41 (488)

FIGURE 14

FR 55 CD 5 8 8 8 5 5 8 5 0

Exonic/nonexonic LD

	Nb pairs	Average intermarker distance	Average LD
Exonic SNPs	36	26 kb	0.65±0.021
Non exonic SNPs	60	36 kb	0.48±0.018
Exonic/Non exonic	96	32 kb	**0.60±0.015**

FIGURE 15

D0855.0052

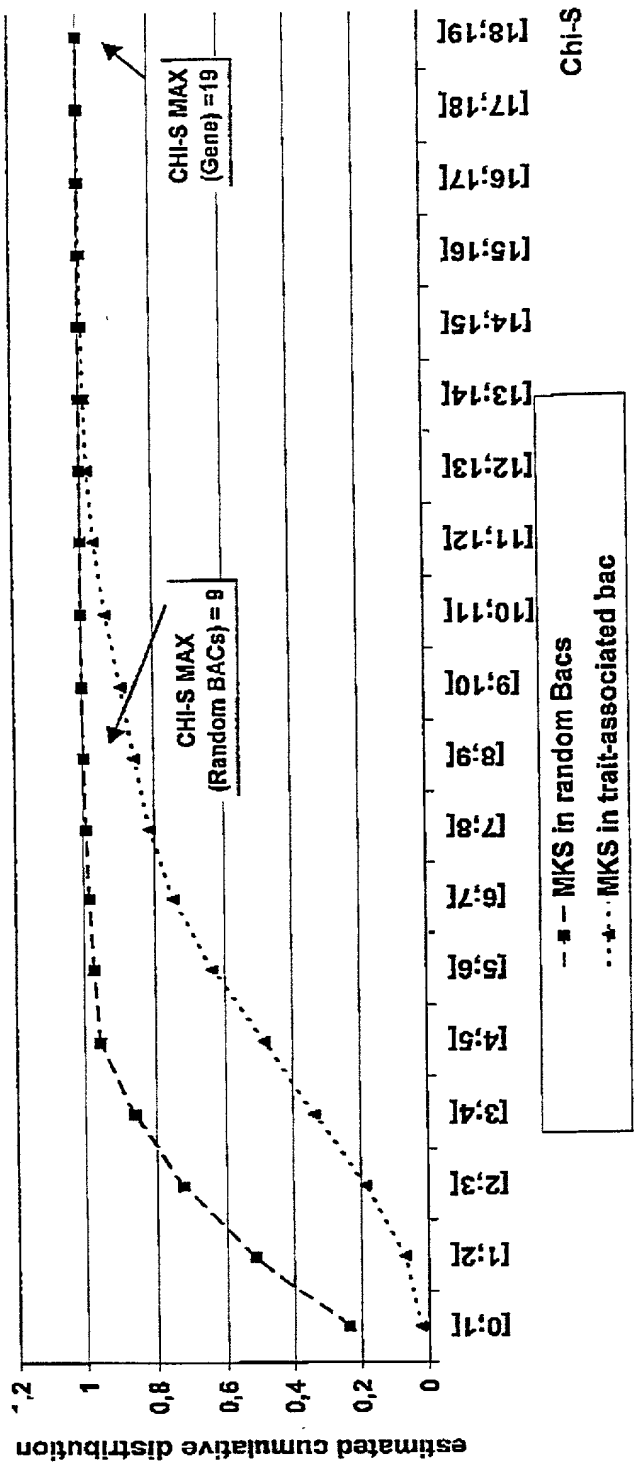

estimated cumulative distribution
1,2
1
0,8
0,6
0,4
0,2
0
[0;1[
[1;2[
[2;3[
[3;4[
[4;5[
[5;6[
[6;7[
[7;8[
[8;9[
[9;10[
[10;11[
[11;12[
[12;13[
[13;14[
[14;15[
[15;16[
[16;17[
[17;18[
[18;19[
Chi-S
CHI-S MAX
(Gene) =19
CHI-S MAX
(Random BACs) = 9
MKS in random Bacs
MKS in trait-associated bac

FIGURE 16 A

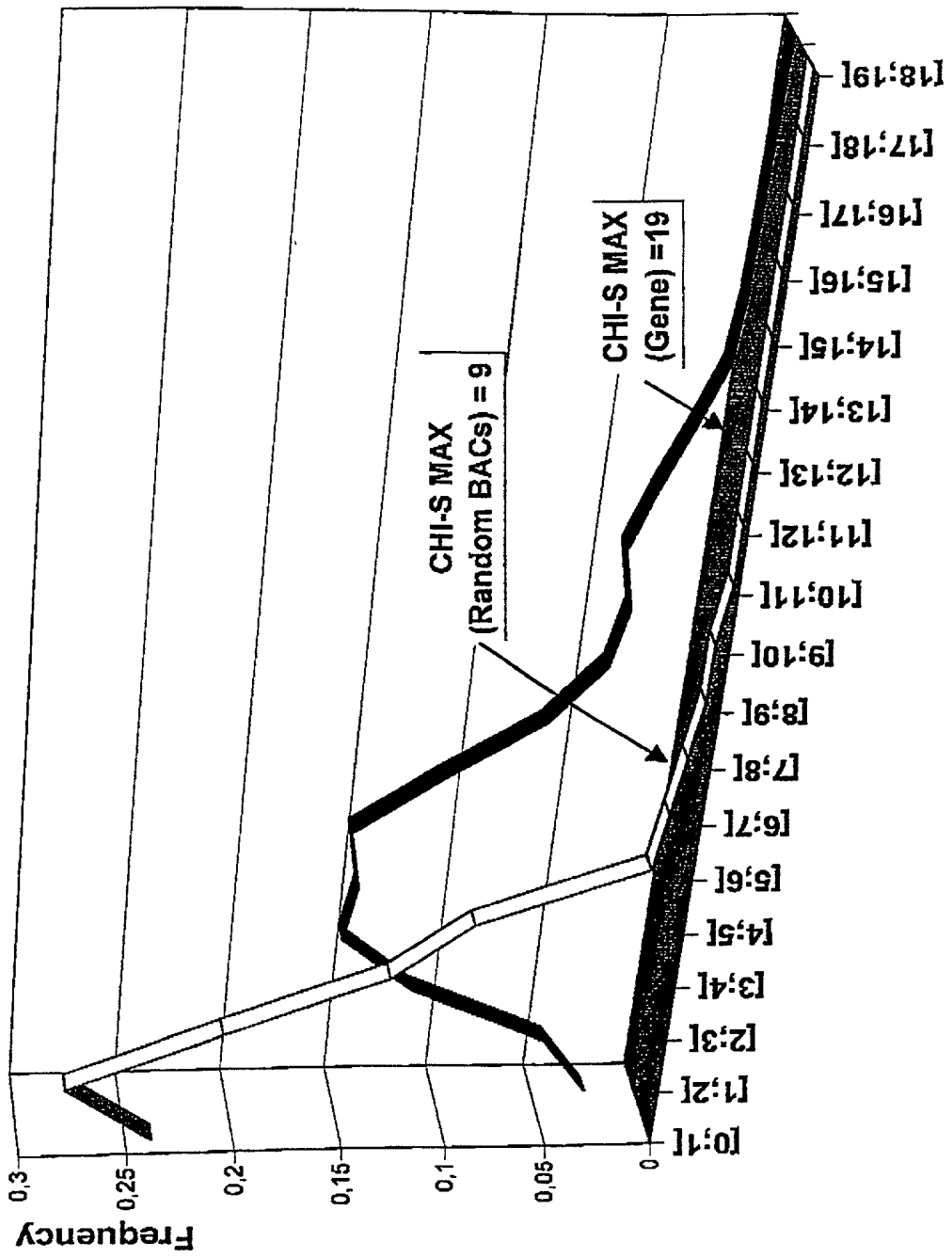

Chi-S
CHI-S MAX
(Gene) =19
CHI-S MAX
(Random BACs) = 9
Frequency
0,3
0,25
0,2
0,15
0,1
0,05
0
[0;1[
[1;2[
[2;3[
[3;4[
[4;5[
[5;6[
[6;7[
[7;8[
[8;9[
[9;10[
[10;11[
[11;12[
[12;13[
[13;14[
[14;15[
[15;16[
[16;17[
[17;18[
[18;19[
MKS in random bacs
MKS in trait-associated bac

FIGURE 16B

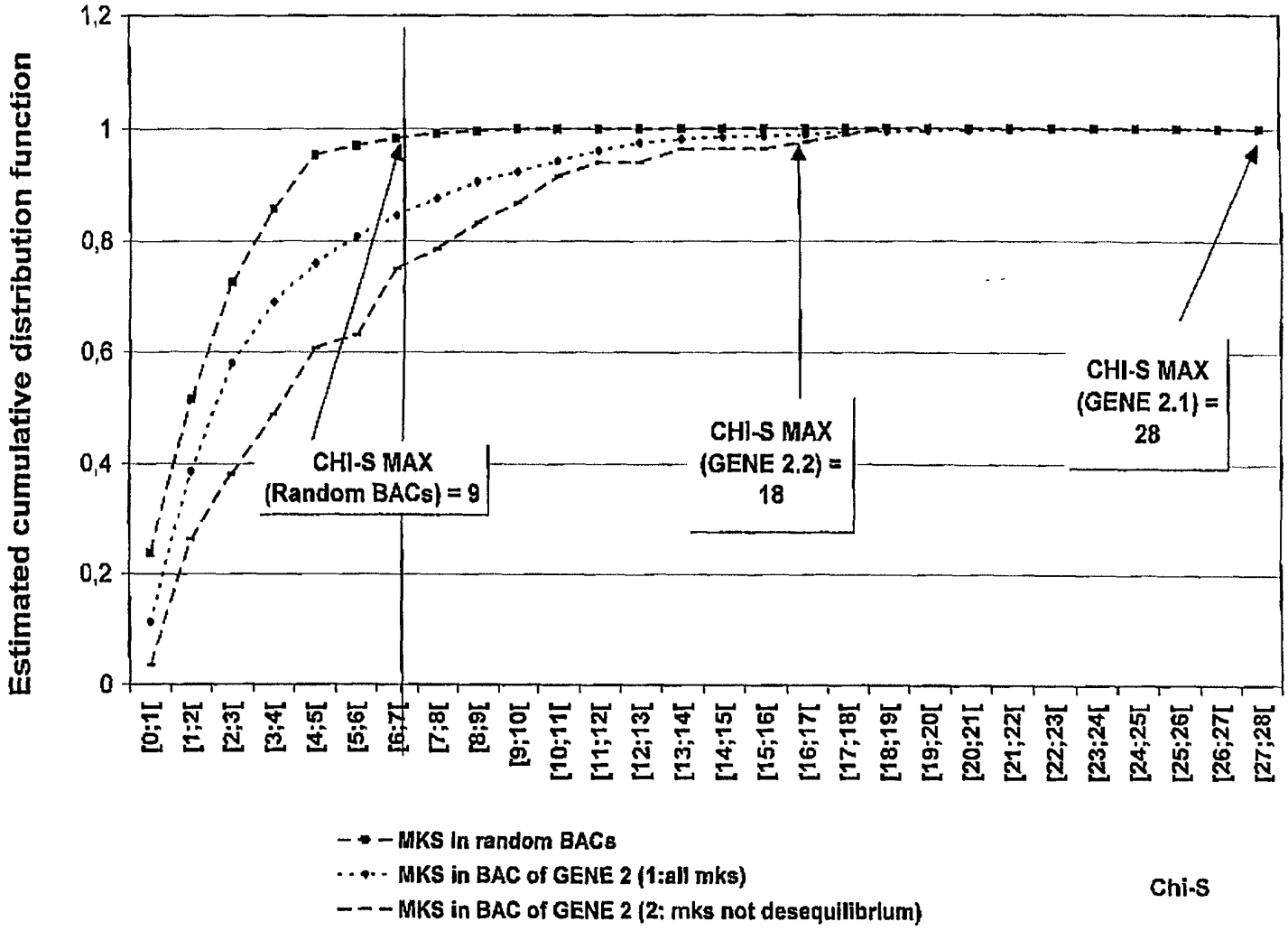

Estimated cumulative distribution function
1,2
1
0,8
0,6
0,4
0,2
0
CHI-S MAX (Random BACs) = 9
CHI-S MAX (GENE 2.2) = 18
CHI-S MAX (GENE 2.1) = 28
[0;1[
[1;2[
[2;3[
[3;4[
[4;5[
[5;6[
[6;7[
[7;8[
[8;9[
[9;10[
[10;11[
[11;12[
[12;13[
[13;14[
[14;15[
[15;16[
[16;17[
[17;18[
[18;19[
[19;20[
[20;21[
[21;22[
[22;23[
[23;24[
[24;25[
[25;26[
[26;27[
[27;28[
MKS in random BACs
MKS in BAC of GENE 2 (1:all mks)
MKS in BAC of GENE 2 (2: mks not desequilibrium)
Chi-S

FIGURE 17A

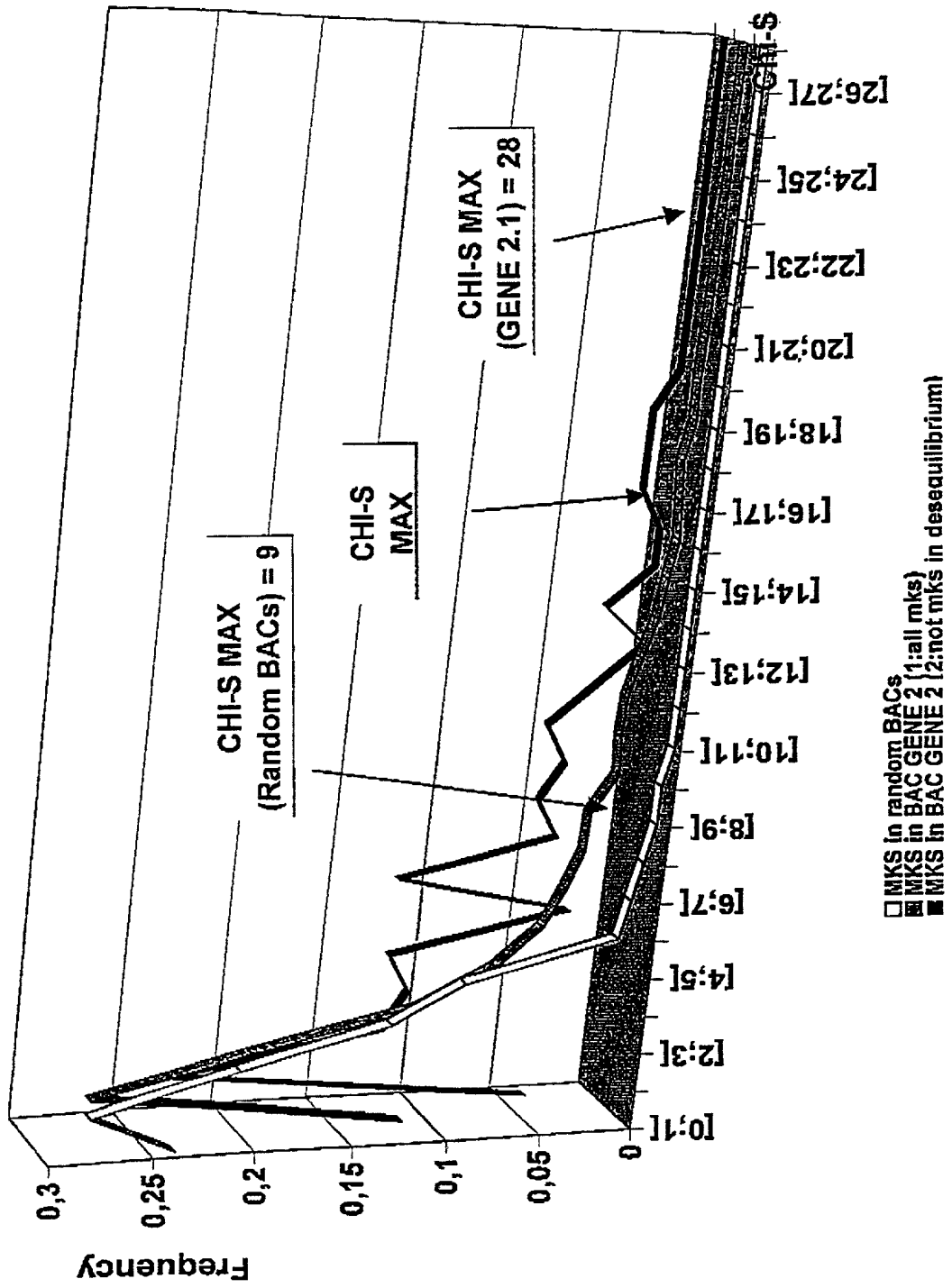

CHI-S MAX
(Random BACs) = 9
CHI-S
MAX
CHI-S MAX
(GENE 2.1) = 28
Frequency
0,3
0,25
0,2
0,15
0,1
0,05
0
[0;1[
[2;3[
[4;5[
[6;7[
[8;9[
[10;11[
[12;13[
[14;15[
[16;17[
[18;19[
[20;21[
[22;23[
[24;25[
[26;27[
CHI-S
MKS in random BACs
MKS in BAC GENE 2 (1:all mks)
MKS in BAC GENE 2 (2:not mks in desequilibrium)

FIGURE 17 B

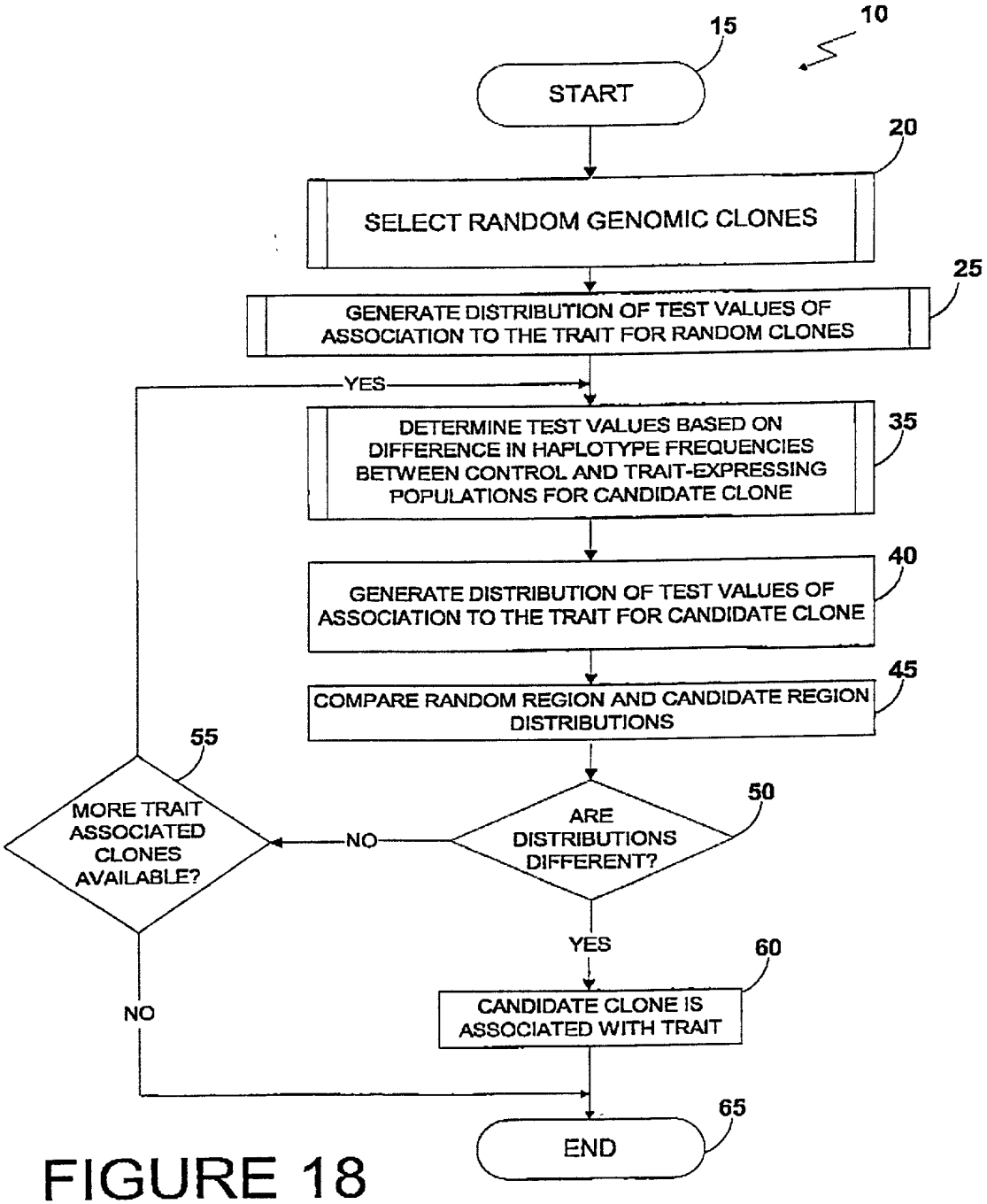


FIGURE 18

FR05450020

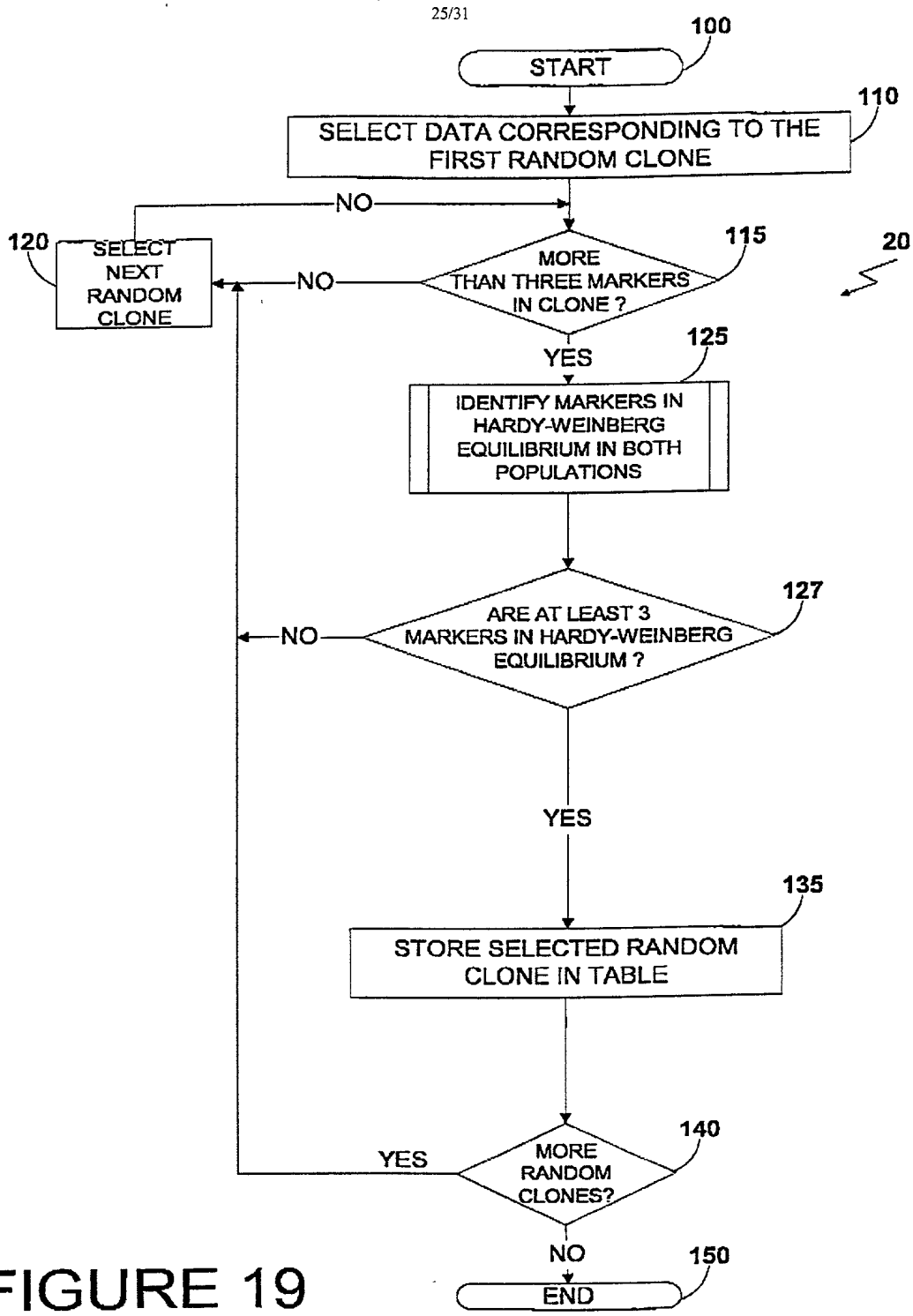


FIGURE 19

09858639 - 052502

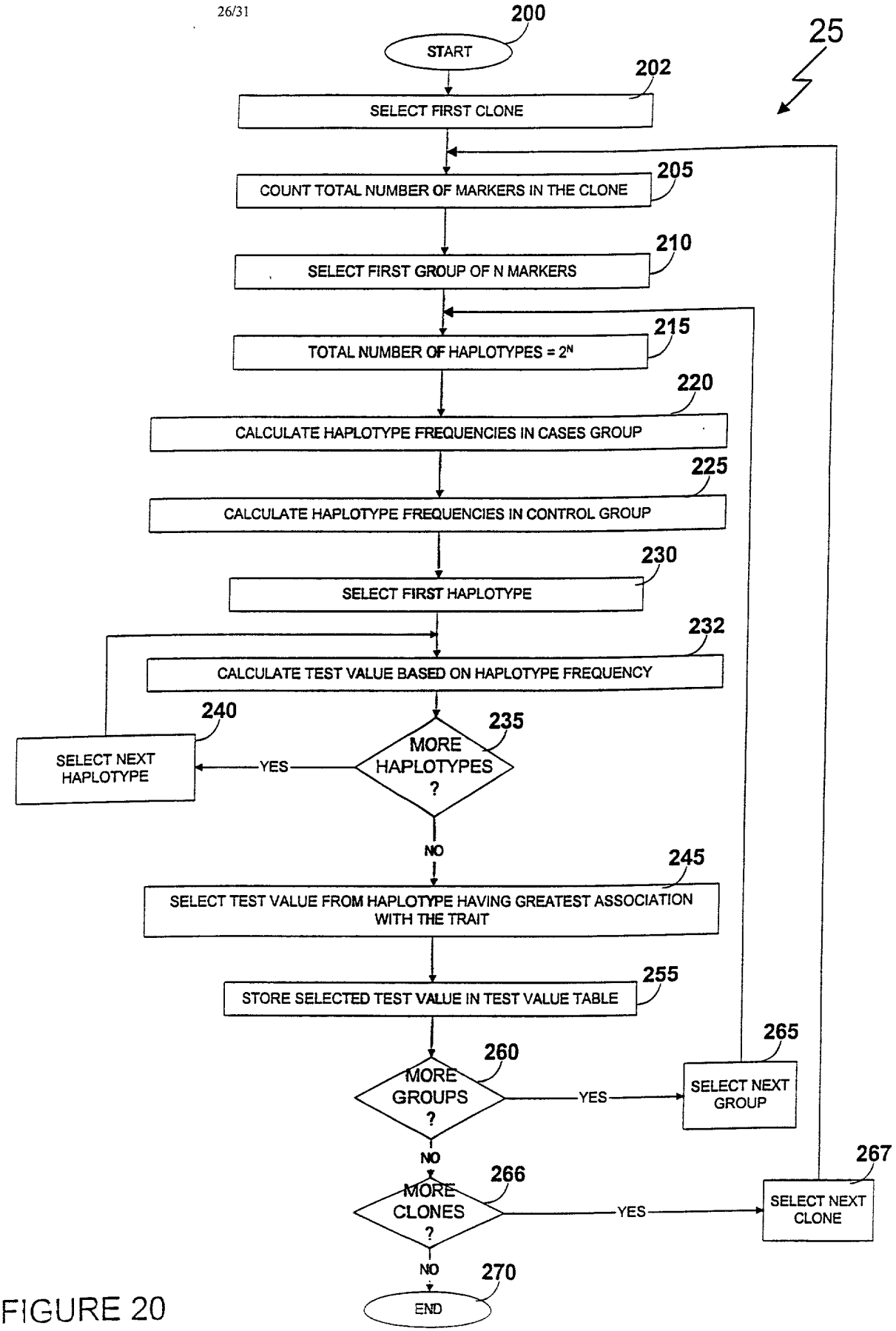

25
200
START
202
SELECT FIRST CLONE
205
COUNT TOTAL NUMBER OF MARKERS IN THE CLONE
210
SELECT FIRST GROUP OF N MARKERS
215
TOTAL NUMBER OF HAPLOTYPES = 2^N
220
CALCULATE HAPLOTYPE FREQUENCIES IN CASES GROUP
225
CALCULATE HAPLOTYPE FREQUENCIES IN CONTROL GROUP
230
SELECT FIRST HAPLOTYPE
232
CALCULATE TEST VALUE BASED ON HAPLOTYPE FREQUENCY
235
MORE HAPLOTYPES ?
YES
240
SELECT NEXT HAPLOTYPE
NO
245
SELECT TEST VALUE FROM HAPLOTYPE HAVING GREATEST ASSOCIATION WITH THE TRAIT
255
STORE SELECTED TEST VALUE IN TEST VALUE TABLE
260
MORE GROUPS ?
YES
265
SELECT NEXT GROUP
NO
266
MORE CLONES ?
YES
267
SELECT NEXT CLONE
NO
270
END

FIGURE 20

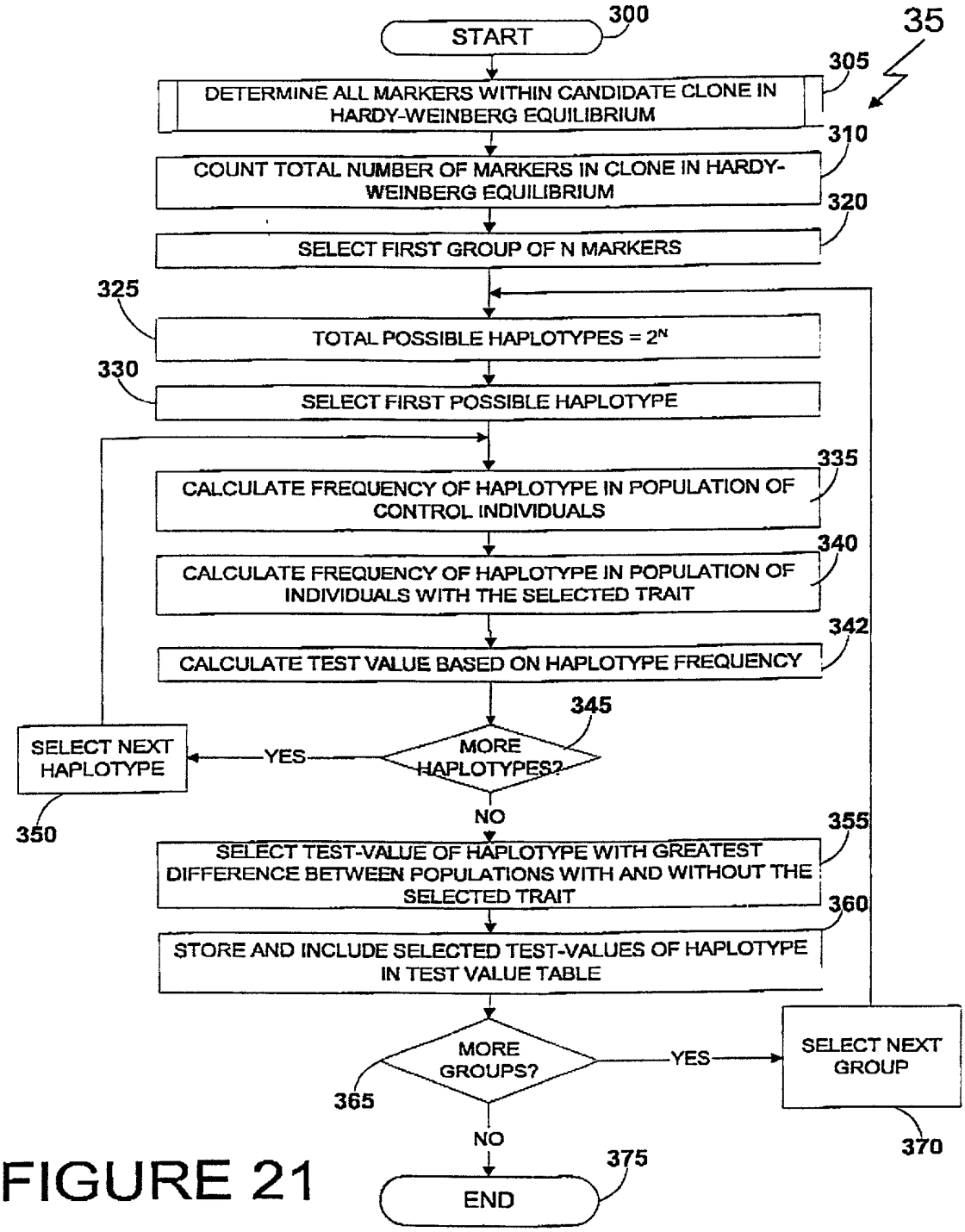


FIGURE 21

Patent 5,965,362

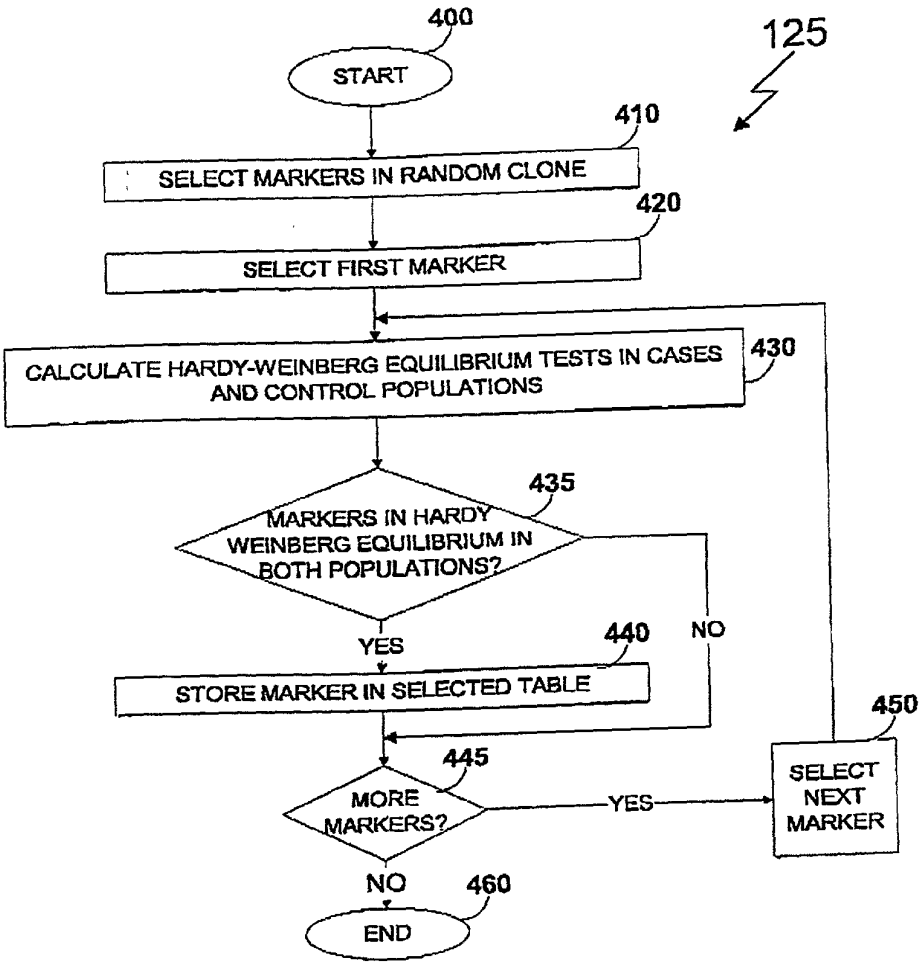

400
START
125
410
SELECT MARKERS IN RANDOM CLONE
420
SELECT FIRST MARKER
CALCULATE HARDY-WEINBERG EQUILIBRIUM TESTS IN CASES AND CONTROL POPULATIONS
430
435
MARKERS IN HARDY WEINBERG EQUILIBRIUM IN BOTH POPULATIONS?
YES
NO
440
STORE MARKER IN SELECTED TABLE
450
445
MORE MARKERS?
YES
SELECT NEXT MARKER
NO
460
END

FIGURE 22

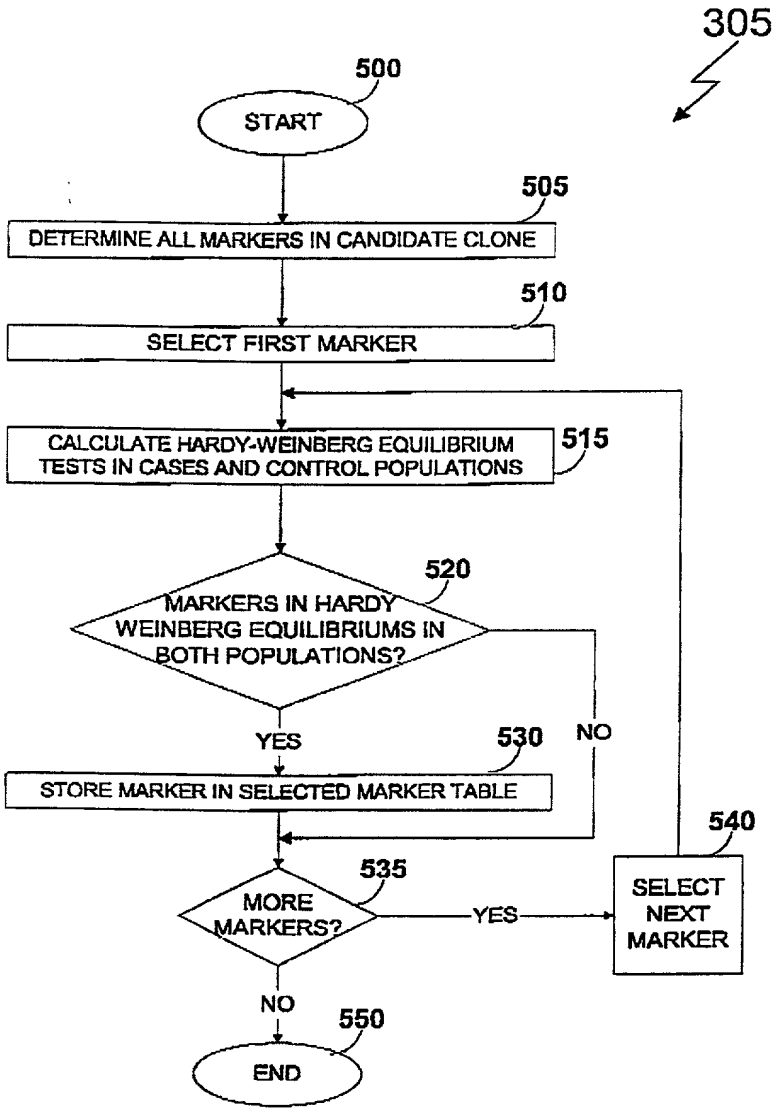


FIGURE 23

ATTORNEY DOCKET NO. 55.US4.DIV

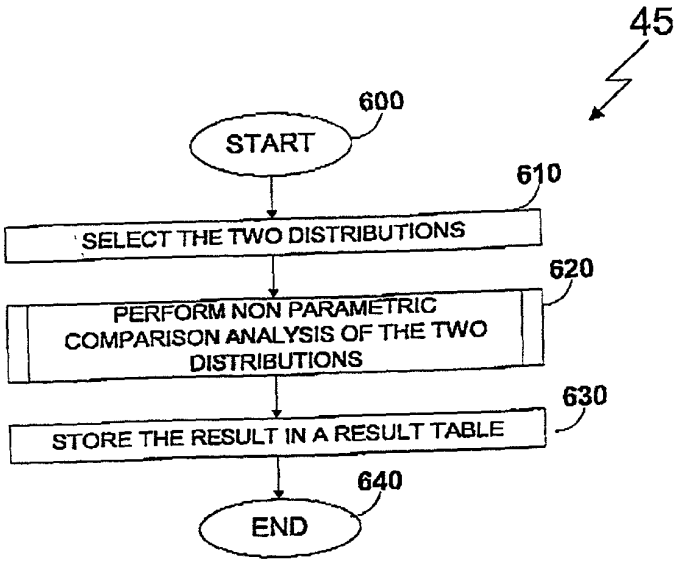


FIGURE 24

09858503 - 050502

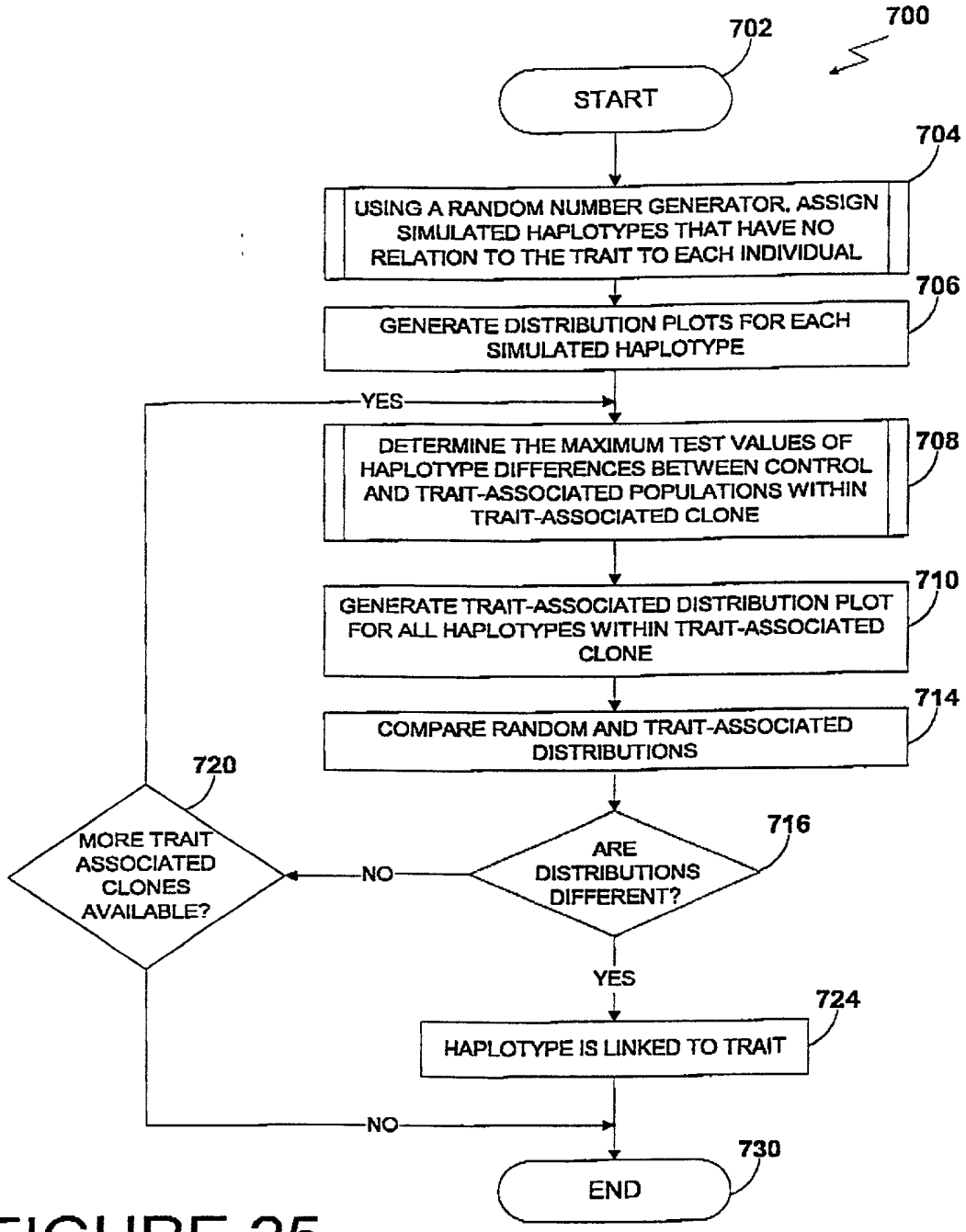

700
702
START
704
USING A RANDOM NUMBER GENERATOR, ASSIGN SIMULATED HAPLOTYPES THAT HAVE NO RELATION TO THE TRAIT TO EACH INDIVIDUAL
706
GENERATE DISTRIBUTION PLOTS FOR EACH SIMULATED HAPLOTYPE
YES
708
DETERMINE THE MAXIMUM TEST VALUES OF HAPLOTYPE DIFFERENCES BETWEEN CONTROL AND TRAIT-ASSOCIATED POPULATIONS WITHIN TRAIT-ASSOCIATED CLONE
710
GENERATE TRAIT-ASSOCIATED DISTRIBUTION PLOT FOR ALL HAPLOTYPES WITHIN TRAIT-ASSOCIATED CLONE
714
COMPARE RANDOM AND TRAIT-ASSOCIATED DISTRIBUTIONS
720
MORE TRAIT ASSOCIATED CLONES AVAILABLE?
NO
716
ARE DISTRIBUTIONS DIFFERENT?
YES
724
HAPLOTYPE IS LINKED TO TRAIT
NO
730
END

FIGURE 25